

ATTACHMENT F

REMARKS

By this amendment, Applicants have amended the claims in a manner which now places this application in condition for allowance. In particular, claims 60-62, 73, 75-77 and 84-85 have been canceled without prejudice or disclaimer. In addition, Claims 50, 51, 57, 68, 86 to 88, 90, 92 and 93 have been amended relative to the previously-provided version, and new claims 98-103 have been included which relate to additional dependent subject matter disclosed in the application, e.g., at pages 1-3, 9-11, and Example 4. In light of these amendments, Claims 50-59, 64-71, 75-77, 79, 81, 83, 86-93, and 98-103 are pending in the present application. In addition, the amended Abstract is provided on a separate page. Applicants submit that the claims as amended are patentable for at least the reasons as set forth below.

In the Official Action, the Examiner has maintained the objection to the Abstract since it is alleged that the "amendment filed on 18 June 2001" was not on a separate sheet as required by 37 C.F.R § 1.72(b). In fact, this amendment (actually filed June 14, 2001) was merely an attempt to add the abstract to the application in response to an improper objection by the Examiner since in fact under MPEP § 1893.03(e), a requirement to add an Abstract on a separate page in a national stage 371 application such as the present case is "improper". However, rather than continuing to expend further time and effort on this point, Applicants overcome the objection by submitting an abstract on a separate sheet herewith. In addition, the clerical error in claim 50 which the Examiner has identified has been rectified, and other minor changes to the claims to be consistent with amended claim 50 have also been made.

In the Official Action, the Examiner has rejected claims 50 to 60, 64 to 71, 73, 75 to 77, 79, 81, and 83 to 93 under 35 U.S.C § 112, first paragraph, on the grounds that the specification, while being enabling for a method of eliciting an immune reaction in a prospective mammalian mother to sperm antigens of a prospective father to alleviate the symptoms of an infertility condition, is not enabling in respect of

- (1) *any* one or more MHC Class I antigens of the prospective father
- (2) *any* one or more antigens
- (3) *any* one or more antigens chosen as the result of being "particularly antigenic and prominent either on the sperm or the conceptus"
- (4) *any* one or more antigens presented in purified or semi-purified form
- (5) *any* modified TGF β , and
- (6) *any* TGF β in which the modification comprises a substitution, deletion or addition mutation or *any* peptide fragment of TGF β .

This rejection, insofar as applied to the claims as amended, has now become moot in that, in an effort to progress the allowance of the present application, the applicants have amended the claims to recite the method which the Examiner has conceded to be clearly enabled. Thus claim 50 has been amended to specify that the prospective mother is exposed to one or more sperm antigens or MHC Class I antigens of a prospective father, and that the MHC Class I antigen is one which is present on leukocytes or in seminal plasma of the prospective father. This amendment is made without addressing the merits of the Examiner's position which Applicants do not concede is correct, and without prejudice to attempts in this or other related applications to overcome the Examiner's arguments and show that the prior position is not justified.

By virtue of the present amendments, amended claim 50 specifies that the TGF β is selected from the group consisting of TGF β_1 , TGF β_2 , TGF β_3 and activin which the Examiner has concurred are fully enabled by the disclosure in the specification as filed (see the Examiner's comments that "the issue is not TGF β_1 , TGF β_2 , TGF β_3 and activin" at page 9 of the Official Action). In addition, Claims 75 to 77, 84 and 85 have been cancelled without prejudice, and thus the rejections to these claims have become moot. Applicants reserve the right to pursue claims to the subject matter of these canceled claims by way of a divisional application if so desired.

In light of the foregoing amendments and arguments, Applicants respectfully submitted that the objections under 35 U.S.C. 112 first paragraph regarding lack of written description in the specification are respectfully traversed and should be withdrawn.

In the Official Action, the Examiner also made minor objections under 35 U.S.C. § 112 second paragraph, with regard to certain claim terms. With regard to the objection to the use of the term "mucosal surface" in claim 51, such an objection is not understood by Applicants since this term does not require an antecedent in claim 50, because it is used for the first time, as clearly evidenced by the singular indefinite article "a", i.e. claim 51 specifies that a mucosal surface of the prospective mother is exposed to one or more antigens. Claim 50 merely states that the prospective mother is exposed to the agents set out in subparagraphs (a) and (b); it is clear from the disclosure in the specification as a whole that this exposure may take place at a variety of sites. Thus claim 51 merely represents a preferred embodiment of the invention. It is requested that this rejection be withdrawn.

Similarly, the objection to claim 68 is not understood; while the Examiner is correct that claim 51, on which claim 68 depends, specifies that "a mucosal surface of the prospective mother is exposed to one or more antigens", claim 68 imposes further limitations regarding the amount of TGF β to which this mucosal surface is exposed. However, the reference to mucosal surface has been deleted so that this is not repeated from claim 51, and in any event, Claim 68 is clearly proper under 35 U.S.C. § 112. The objection to Claim 60 has become moot by the cancellation of this claim. It is thus submitted that all prior objections under 35 U.S.C. § 112 are traversed and should be withdrawn.

In the Official Action, the Examiner rejected Claims 50-60, 64-67, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 under 35 U.S.C. § 103(a) as being unpatentable over US Pat. No. 5,395,825 to Feinberg, in view of the Clark et al. 1994 article and the Chaouat et al. 1985 article. This rejection is respectfully traversed. In the Official Action, the Examiner has previously stated that one cannot show nonobviousness by "attacking references individually" if the rejections are based on combinations of references. It is respectfully submitted that the Examiner is incorrect. In the first place, the previous arguments by the Applicants were not "attacking references individually" but showing in particular why the Examiner's position as to the teachings of the references was *incorrect*. If the Examiner is *incorrect* as to her interpretation of one or more of the references, clearly the alleged combination of references which are asserted to show obviousness is *also* incorrect since such combination relies on false assumptions.

Secondly, it is well established that the Examiner *cannot* "pick and choose" from a reference only those teachings which support a certain position, but instead must look

at the prior art as a whole. As the Federal Circuit has held in the case of *In re Hedges*, 228 USPQ 685 (1986):

"It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it which will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference suggests to one of ordinary skill in the art."

As detailed in Applicants' prior responses, the Examiner has misinterpreted the reference by Chaouat et al and Clark et al., for the reasons as set forth in the attached first Declaration of Professor David Clark, filed herewith as Attachment C. As set forth in Dr. Clark's Declaration, taking into account all of the relevant teachings at the claimed priority date of the present invention, it simply would not have been obvious to combine the teachings of Feinberg et al, Clark et al and Chaouat et al. in the manner set forth by the Examiner so as to come up with the invention as presently claimed.

In particular, Applicants submit that it would be evident to the person of ordinary skill in the art that the paper by Clark et al in fact describes a cell culture study performed on tissue cultures derived from decidua obtained from samples obtained at termination of "*apparently normal*" pregnancies at 9 to 12 weeks gestation. Thus these samples were of *maternal*, not fetal origin, and there was no suggestion that the women whose pregnancies were terminated were suffering from infertility of any kind. The discussion in the Clark paper thus relates solely to the possibility that the TGF- β like molecule disclosed therein might be associated with improved survival of the fetus following implantation. There is no disclosure or suggestion that this TGF- β like molecule could be beneficial in the treatment of infertility. Moreover, this paper does not suggest that the TGF- β like molecule had any activity *in vivo*.

Even further, the paper by Chaouat et al is **not** directed to **any** method of treatment; it was solely aimed at producing an animal model. Moreover, results presented in this paper clearly show that immunization of female mice with cells of the paternal MHC Class did *not* result in reduced fetal wastage. It was suggested that the reduction was a result of active suppression of NK cell activity, rather than induction of T-cell tolerance. Dictionary extracts illustrating the difference between innate NK-mediated responses and induction of immunological tolerance are submitted herewith as Attachment D.

Accordingly, there clearly would have been no motivation for a person of ordinary skill in the art to combine the teachings of either Clark et al or of Chaouat et al with those of the Feinberg patent, or to combine Clark et al with Chaouat et al. to begin with.

Moreover, contrary to the position of the Examiner, at the priority date of the present invention, it was accepted in the art that immunizing with paternal antigen was *not* beneficial in treating infertility. This is evidenced for example in the papers by Illeni et al, Fraser et al, Ho et al, and Cauchi et al, annexed to Professor Clark's declaration as Exhibits A-C and submitted herewith. In addition, in a report of a large collaborative multi-center study funded by the US National Institutes of Health, it is recommended that immunization with paternal antigen alone **should not be used**. This study was published in 1999, i.e. a **year after** the international filing date of the present application, and **two years after its priority date**. A copy of this report is annexed as Exhibit D to Professor Clark's declaration submitted herewith. Thus even long after the date of making the invention, the general opinion in the art **taught away** from the claimed invention.

Accordingly, Applicants respectfully submit that the Examiner is not only interpreting two of the references incorrectly; she is assuming that there is motivation to combine them in the light of the knowledge generally available to one of ordinary skill in the art at the claimed priority date. However, contrary to the Examiner's assumptions, the references submitted herewith to show the true state of the art before and after the priority date of the present invention clearly show that such motivation is **completely absent**, and that such references **teach away** from the claimed invention. The interpretation of the references giving rise to the outstanding rejection is thus incorrect and could only have been made using a reconstruction based on hindsight reasoning, and such a rejection is improper on that basis as well.

The Examiner also rejected dependent Claims 66-67, 71, 75, 76, 83-85 and 92 on combinations of references based on Feinberg US Patent 5,395,825, Clark and Chaouat as described above, and these rejections are traversed for the same reasons as stated above. Moreover, in light of the fact that the independent claim 50 in its amended form is not anticipated or made obvious by the cited references, the dependent claims are patentable over the cited references as well. In addition, the Examiner's rejection of claim 92 on the basis of the paper by Heidenreich et al, is improper because this reference teaches a method of detecting anti-sperm antibody in infertile *males*. The mere detection of anti-sperm antibody in infertile *men* is irrelevant to treatment of infertility in *women*. Once again, it is respectfully pointed out that there would be no motivation for adding the step of testing for the presence of anti-sperm antibodies *without* prior knowledge of the invention as defined in claim 50. Accordingly,

the prior art rejections of the Examiner can only be made using hindsight analysis, and such rejections are also respectfully traversed and should be withdrawn.

It is also noted that the Examiner has conceded that claims 68, 69, 87, 88 and 91 are free of the prior art, and this concession is acknowledged with appreciation.

In short, none of the cited references disclose or suggest the specific features of Applicants' claimed invention, as particularly embodied in amended Claim 50 and its dependent claims, and thus the outstanding prior art rejections, insofar as applied to the claims as amended, are respectfully traversed and should be withdrawn.

As a final matter, Applicants submit references via an Information Disclosure Statement which have just come to light. However, these references have no bearing on the patentability of the present claims for at least the reasons as discussed in the attached Second Statutory Declaration of Dr. David Clark, submitted herewith as Attachment E.¹ In short, these references actually teach away from the present invention and as conceded by the authors provide no more than an invitation to conduct further experimentation.

In light of the amendments and arguments as set forth above, Applicants submit that the present application overcomes all prior rejections and has been placed in condition for allowance. Such action is earnestly solicited.

END REMARKS

¹ The executed copies of the Declarations of Dr. Clark are being forwarded to Applicants' counsel and will be filed shortly.